KIDNEY TRANSPLANTATION IN A DEVELOPING ECONOMY: CHALLENGES AND INITIAL REPORT OF THREE CASES AT ILE-IFE

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ABSTRACT:

**Background:** Kidney Transplantation (KT) is globally adjudged the best alternative treatment for end stage renal disease (ESRD) in preference to life-long dialysis. This form of therapy was hitherto unavailable in Nigeria until our hospital and a private hospital embarked on KT programme in the face of our depressed economy with inadequate facilities. We present initial report of KT performed in our hospital and the challenges of KT in our developing society.

**Cases Report:** Three patients with ESRD had living related KT between June 2002 and April 2003. The first patient died with functioning graft 6½ months post-transplantation from complications of diabetes mellitus and sepsis, while the remaining two still enjoy good quality of life 35 months post-transplantation. There were problems with procurement and monitoring of immunosuppressive drugs in the three patients. This report also illustrates common causes of ESRD in Nigeria and some of the complications of KT. To our knowledge, this is the first reported cases of KT in Nigeria.

**Conclusion:** Kidney transplantation is cost effective and offers good quality of life for ESRD patients. Poverty, inadequate facilities and lack of donors are major problems facing KT in our society. Although KT requires high technical and material resources, with proper training, commitment and adequate funding, it is feasible, safe and cheaper on a long term basis for the management of patients with ESRD in a developing economy like ours. There is a need of government funding of KT program in developing countries.

**Key Words:** Kidney Transplantation, Living related donors, End stage renal disease, Haemodialysis and Developing Economy.
INTRODUCTION:

The excretory function in chronic renal failure (CRF) is greatly reduced such that with the disease progression to an end stage renal disease (ESRD) (creatinine clearance <5ml/min) the patients become life-dependent on renal replacement therapy. Although haemodialysis (HD) and peritoneal dialysis (PD) are good alternatives for treating these patients, since 1954 after the first successful long-term kidney transplantation (KT) in Boston, USA, KT has become the vogue in the treatment of ESRD in many parts of the world due to better quality of life, longer survival and the cost effectiveness ¹,². Although many privileged Nigerians have had KT, prior to now these procedures were exclusively carried out overseas until our teaching hospital and a private hospital recently initiated KT programme locally. In Nigeria, the leading causes of CRF and ESRD are hypertensive nephrosclerosis and chronic glomerulonephritis ³,⁴. There are indications which suggest increase in the incidence of these diseases, which implies that increasing numbers of Nigerians may develop CRF and subsequently require treatment for ESRD. In the face of low income and scarcity of HD facilities and personnel’s, the traditional treatment of ESRD in our community with HD requires enormous wealth, courage, perseverance, time and sacrifice. As in other developing nations, these frequently pose major constraints in the effective management of ESRD patients in our community. The long term cost implication, loss of man work hour, quality of life and the psychological stress of being machine dependent associated with HD; suggest that KT is a better alternative to treat our ESRD patients ¹. Although our centre is the pioneering public teaching hospital with KT programme in our country, and relies mainly on local personnel’s, we are still faced with major constraints hindering regular transplantation. This report highlights our experience with the first three patients transplanted in our Institution and the challenges of KT in our developing society. It also illustrates the major causes of ESRD in our community. To our knowledge, this is the first reported cases of KT in Nigeria.
CASE REPORTS:

Case 1: Mr O.O is a 40yr old businessman, a known hypertensive and diabetic, was referred to us May 2nd 2002 with a 4month history of generalised body swelling, breathlessness, pruritus, nausea and vomiting. After clinical and laboratory evaluation, he was confirmed as a case of chronic renal failure in ESRD. Other problems on presentation include lobar pneumonia, thrombophlebitis, hypertension (BP 210/120) and poor glycaemic control. After sessions of HD with proper control of sepsis, hypertension and diabetes, he was worked up and transplanted with kidney donated by the junior brother on June 26th 2002. Postoperatively he was placed on triple therapy (cyclosporine, prednisolone and azathioprine). The urine production was spontaneous with gradual decline in the preoperative creatinine and urea levels of 752mmol/l and 10.2mmol/l respectively to normal levels within 10 days. He had wound sepsis with secondary closure on postoperative day 13. Two months after surgery, he developed viral conjunctivitis, oral moniliasis, and sharp pep-perish epigastric pain for which gastro-duodenoscopy confirmed acute antra gastritis and chronic atrophic gastritis with deformed duodenal cap. There was no malignancy and no infection with helicobacter-like organism. He was treated with antacid, H2-receptor blocker and antifungal drugs with good response. Throughout treatment, the allograft function remained normal. Apart from periodic poor glycaemic control, he remained stable until 3½ months postoperative when he exhausted the initial free immunosuppressive drugs and he could not afford to buy more. The following 24hr urine output subsequently dropped to 1.3L, followed by a period of anuria over 18hrs by which time the urea and creatinine levels gradually rose to 12.7 and 216mmol/l respectively. The delayed acute rejection was quickly reversed with heavy dose of hydrocortisone and cyclosporine with immediate returns of urea and creatinine back to normal levels. He continued with immunosuppressive drugs and remained stable until 4½ months postoperative when he was readmitted because of septicaemia and diabetic hyper-osmolar non-ketotic coma, with features of autonomic neuropathy and bone marrow suppression (evidenced by pan-cytopenia). The fluctuating blood sugar (ranged 130-487mmol/l) and the hypokalaemia were getting controlled when he became psychologically depressed and subsequently refused food and drugs. His condition continued to deteriorate until he was certified dead 6½ months post-transplantation with functioning allograft, which till the last day was making over 3L of urine. The autopsy result confirmed marrow depression/fatty infiltrations, evidence of chronic peptic ulcer with opportunistic infection in the gut, and vascular complications of diabetes. Histopathology of the allograft confirmed normal kidney.
Case 2: Mr O.A is a 35yr old teacher with CRF in ESRD secondary to chronic glomerulonephritis diagnosed 6months earlier and already on HD from the referral hospital. Other salient problems on presentation include acute pulmonary oedema with pleural effusion, uraemic pericarditis, and uraemic gastritis with melaena stool, chronic pyelonephritis, anaemia and hypertension. He was resuscitated and worked up for renal transplantation that took place April 6th 2003. His junior brother donated the allograft. Postoperatively, he was placed on cyclosporine, prednisolone and azathioprine. The initial urine output average 1.26L daily for 2days after which the daily output increased sharply to 8 litres, and then gradually reduced to 4L/day. The urea and creatinine levels gradually declined to normal from the preoperative levels of 18 and 951mmol/l respectively. Complications of surgery include wound sepsis with dehiscence, femoral vein thrombosis, lymphocoel, lymphoroea with lymph-oedema, urethritis and retrograde epididymo-orchitis. He was managed conservatively with antibiotic, wound dressing, and anti-thrombotic agent (clexane). The wound was secondarily closed 3 weeks after surgery and the lymph-oedema cleared few days later. Till date, 35months after surgery, his condition has remained stable with adequate daily urinary output and normal electrolytes and urea profile without need for HD.
Case 3: Miss E. O, a 30-year-old teacher suddenly developed progressive leg swelling and diminution of urine output of 5months duration. She later developed generalised body weakness, nausea, anorexia, vomiting, hiccoughs, disorientation and coma. She regained consciousness after sessions of HD in a teaching hospital before she was referred to us on the 3rd of March 2003. On presentation, she had severe hypertension (BP 230/120), congestive cardiac failure, lobar pneumonia, severe anaemia with packed cell volume (PCV) of 23% and moderate-severe weight loss (body weight was 33.5kg). Her daily urinary output ranged 10-20ml. Her haemoglobin genotype was AA and she was neither a known hypertensive nor diabetic. She is the second of seven children in a monogamous setting. She was placed on antihypertensive drugs, digoxin, antibiotics, iron supplement, erythropoietin and counselled for renal transplantation. Her body weight and PCV were built to 38kg and 39% respectively. She was fully investigated, stabilised, and transplanted with kidney donated by her mother on the 23rd of April 2003. Postoperatively, she was maintained on triple immunosuppressive regimen (cyclosporine-A, azathioprine and prednisolone). She had prolonged allograft dysfunction for about 50days during which the kidney was making about 400ml of urine per day and was stabilised on HD. Monoclonal antibody (OKT3), tacrolimus and mycophenolate (MMF) were introduced when biopsy result indicated vascular rejection. Thereafter, between postoperative day 50 and 60, the daily urine output increased to 750-800ml, and later increased sharply to 1.5-3.5L/day till date. Azathioprine was permanently withdrawn from the immunosuppressive regimen when she developed sign of marrow depression. Apart from mild hirsutism, there was no other sign of drug reaction. Twenty months after surgery she had painful ovarian mass for which she had cystectomy. She has been followed up for 34½ months and she has remained stable with well-controlled blood pressure and normal renal function. Her packed cell volume is currently 40% and her body weight 56kg.
DISCUSSION:
The three cases above illustrate the three commonest aetiological factors of CRF and ESRD in Nigeria. ESRD, the main indication for kidney transplantation, is the ultimate end stage of the pathological process that follows CRF, which may be secondary to chronic glomerulonephritis (CGN), hypertensive nephrosclerosis or diabetic nephropathy etc. In our environment, glomerulonephritis appear commoner than the hypertensive nephropathy. The first patient suddenly developed generalised body swelling after which diabetic nephropathy was confirmed. The disease apparently progressed asymptomatic until it manifested as ESRD. The second and third cases illustrate unusual cases of chronic glomerulonephritis and hypertensive nephropathy in young Nigerians. In both patients, the ESRD also manifested suddenly. The pathological process in CRF is slowly progressive and most patients become symptomatic when the glomerular filtration rate is less than 30%.

The donors and recipients were thoroughly evaluated to exclude systemic diseases including malignancy. The three recipients and their respective donors had ABO blood group and human leucocytes antigens (HLA) typing. Mismatch of the ABO and sensitisation to HLA complex can result in hyper-acute rejection. Other investigations include serology tests to exclude infectious diseases (like hepatitis B & C, cytomegalovirus and HIV infection) which may have major consequence on the recipient post transplantation, endoscopies to exclude gastro-duodenal ulcer and occult gastrointestinal or bladder malignancies in the recipients and selective renal angiography to determine the number and nature of the renal arteries and veins in the donors, as this would determine the number of vascular anastomosis to be carried out and influence the duration of operation, particularly the warm ischaemic time. It will also help to identify and prevent injury to major aberrant vessels to the kidney during harvesting.

In all the three living donors, flank incision with 12th rib resection was employed to harvest the kidney extra-peritoneal. We prefer this approach because it offers adequate exposure with good access to the organ without the risk of peritoneal contamination or injury to the intra-peritoneal organs. Trans-abdominal approach is favoured by some because it offers better access to the renal vessels with minimal handling of the organ. Although Collins C2 or Euro-Collins are preferred intracellular electrolyte flush solutions; immediately after harvesting, ice-cold ringer’s lactate solution which was locally available was used to perfuse the organs for rapid cooling to reduce cellular metabolic demands and to rid the organ of blood, after which the organs were immediately transplanted. In each recipient, the renal vein was
anastomosed with the external iliac vein while renal artery was anastomosed with the internal iliac artery. Ureteroneocystostomy technique was adopted to implant the ureters in the host bladder. Postoperatively, the second recipient had wound sepsis and dehiscence, femoral vein thrombosis, mild lymphocele, lymphorhea and lymph-oedema, all of which were managed conservatively. Preoperative femoral vein canulation for HD could be responsible for the thrombosis. The other two recipients had no major complications.

Side-effect of immunosuppressive drugs manifested in the three recipients especially the first patient who developed overwhelming sepsis with opportunistic infection and later succumbed to complications of diabetes. His peptic ulcer disease was also aggravated by the immunosuppressive. Diabetes has been known to have negative impact on patient’s performance post-transplantation. Apart from immuno-suppression, diabetics are also prone to coronary arterial disease, a major cause of mortality in transplant patients. Hirsutism and marrow suppression observed in the third patient were due to cyclosporine and azathioprine respectively. The hirsutism cleared significantly when the dose of cyclosporine was reduced, while the marrow suppression also improved when azathioprine was substituted with mycophenolate. Although the delayed allograft function in this patient was attributed to vascular rejection, it could in part be due to cyclosporine toxicity, because after biopsy specimen of the allograft showed normal histology, the allograft was still making inadequate urine until cyclosporine was substituted with tacrolimus in the drug regimen. Lack of drug assay facilities to monitor the blood level of these drugs constituted major constraints in the administration of drugs particularly the cyclosporine. To avoid drug overdose and toxicity, all the patients were maintained at the lower recommended safe dose.

The delayed acute rejection in the first patient occurred when he exhausted the three months free immunosuppressive drugs and he could not afford to buy more. Apart from the preoperative care partly financed by the three patients, the cost of operation, postoperative care and the initial supply of immunosuppressive drugs were borne by our hospital because these patients could not afford the cost. However, our hospital policy was to provide the initial 3 months maintenance immunosuppressive drugs after which the patients bear the cost. In the face of rejection, we were compelled to procure more immunosuppressive for this patient.

There were no major surgical complications in all the three donors. One of them, an obese patient, had superficial wound sepsis, which delayed his hospitalisation to 14th-day post-
nephrectomy. The other two were discharged on post-operative day 5 and 6. Although all the three donors underwent psychiatry examination before surgery, two of them still exhibited anxiety state postoperative. Post donation anxiety is a recognised symptom in transplant donors hence the need for proper psychological evaluation before donation\textsuperscript{10}.

Risk of operative complications in living donors with possible loss of organ in case of allograft rejection makes cadaveric donors more attractive in many nations with established transplantation programmes. Apart from operative complications, no major long-term problem has been reported in most live donors\textsuperscript{11-13}. Major fear is the suggestion that fifty percent reduction in renal mass may lead to glomerular hyper-filtration, progressive glomerulosclerosis and deterioration of function in the remaining kidney that may result in proteinuria and hypertension\textsuperscript{13-15}. However, in series involving more than 600 living donors, increased frequency of either significant hypertension or renal insufficiency were not demonstrated as long as 20 years after uni-nephrectomy\textsuperscript{14, 16, 17}.

Living donors were used in all our cases because only this is possible in this early stage. Use of cadaver donors will requires a more comprehensive national programme with legislation and nation-wide coordination. As in most established centres, availability of suitable donors still poses major constraint to our KT programme, even parents and siblings of patients with ESRD were sceptical to donate. It is our hope that with public education and increase public awareness, the anxiety of our people will be allayed, while effort is intensified towards the use of cadaver donors. Success with the use of xenografts and organ cloning may solve the global shortage of donors in the near future.

Apart from the lingering problems of funding and suitable donor, we have overcome some other maiden problems we faced at the commencement of the programme. As of today, our non-functioning old fluoroscopy machine have been replaced with new one, a new colour doppler ultrasound has also been procured, and a tissue typing laboratory has been set up to reduce cost and enhance the investigations and monitoring of these patients.

Our patients enjoyed superior quality of life post-transplantation compared to HD. The three patients particularly felt relieved from thrice weekly HD. Despite the huge expenses also incurred on initial overseas importation of immunosuppressive drugs and the HLA-typing abroad, there is also significant cost benefit compared to HD.
After 35 months of follow-up, the last two patients have remained stable and have thence resumed normal activities without the need for HD. Our relative inactivity since the last transplantation almost 3 years ago was because our patients could not afford the cost of the procedure which currently stood at 1.7 million naira ($12,300:00 US). This includes the cost of tissue typing and other investigations, preoperative care including HD and 3-month supply of immunosuppressive drugs postoperative. Many of our patients died because they could not even afford the cost of regular HD. Few patients that were fortunate to get sponsorship from government or religious bodies could not get suitable donors.

This review highlights the challenges of KT in our developing economy and also illustrates some of the complications of KT and the common aetiology of ESRD in Nigeria. Until self-reliance on tissue typing and local production of immunosuppressive drugs to reduce cost is fully attained by developing nations, the cost of KT may remain unaffordable by most of our patients with ESRD. Consequently, the much-desired better quality of life with this form of therapy may continue to elude many of our patients and thwart our effort at improving the care of patients with ESRD in our developing community.

CONCLUSION: Kidney transplantation is effective and economical. Lack of willing donors, poverty and inadequate facilities constitutes major setback to KT programme in our developing society. Although the procedure is highly technical and demands high level of coordination of human and material resources; with adequate funding, commitment, proper training and provision of basic infrastructures, it is safe, feasible and cheaper on a long term basis for the treatment of ESRD in a developing economy like ours. To benefit most patients with ESRD, there is a need of government funding of KT program in developing countries.
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